"Contains NO CBI"

UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001

August 27, 1992

(A)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

8EHQ-92-12122
INIT
8892001036O

92 SEP -1 AM 11: 39

Document Processing Center (TS-790)
Room L-100
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

Re: CAP Agreement Identification No. 8ECAP-0110

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith submits the following report pursuant to the terms of the TSCA §8(e) Compliance Audit Program and Union Carbide's CAP Agreement dated August 14, 1991 (8ECAP-0110). This report describes mechanism of action studies concerning convulsions produced by UCON® 50-HB-400 (CASRN 9038-95-3).

"Studies Into the Mechanism of Action of Convulsive Seizures Produced by UCON 50-HB-400", Mellon Institute of Industrial Research, Report 25-43, May 28, 1962.

A complete summary of this report is attached.

Previous TSCA Section 8(e) or "FYI" Submission(s) related to this substance are:

8EHQ-1086-0635

Previous PMN submissions related to this substance are: (None)

RECEIVED 2/15/95

25-43

This information is submitted in light of EPA's current guidance. Union Carbide does not necessarily agree that this information reasonably supports the conclusion that the subject chemical presents a substantial risk of injury to health or the environment.

In the attached report the term "CONFIDENTIAL" may appear. This precautionary statement was for internal use at the time of issuance of the report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Yours truly,

William C. Kuryla, Ph.D.
Associate Director
Product Safety
(203/794-5230)

WCK/cr
Attachment (3 copies of cover letter, summary, and report)

SUMMARY

Confidential

Report 25-43

R: 5-28-62

5-29-62

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

SPECIAL REPORT

Studies Into the Mechanism of Action

of Convulsive Seizures Produced by UCON 50-HB-400

Union Carbide Chemicals Co., U.C.C. Industrial Fellowship 274-25

In order to study the physiological mechanisms responsible for the reported convulsions produced by UCON 50-HB-400, a few representative members of the 50-HB series were investigated. The chemicals studied were UCON 50-HB-55, 50-HB-260, 50-HB-400, and 50-HB-5100. All of these were studied in rats, mice, and frogs; while the latter two chemicals were also investigated in dogs.

None of the UCONS selected produced any excitatory effect in frogs, in fact, lethal doses were always preceded by marked central nervous system depression. This was an unfortunate finding as the frog lends itself well to a study of the central site of action.

Procter & Gamble data showed selective C.N.S. stimulation in rats for members of this series up to the 50-HB-660. Higher molecular weight members and members of the LB series failed to produce such symptoms. We have confirmed their findings and showed positive effect with the 50-HB-55, 50-HB-260, and 50-HB-400 UCONS, and negative effects with the 50-HB-5100 in mice (20-25 gm. females), and rats (200-250 gm. females). The minimal active dose in both species for these compounds was 0.5 ml./kg. administered intraperitoneally over a wide range of concentrations. Tremors were observed at lower doses. All four UCONS were also investigated for their ability to induce a convulsive seizure after oral administration to rats. Lethal doses of each were given to groups of five animals. All of the animals treated with 50-HB-55, 260, or 400 showed excitation or a definite well defined convulsion preceding death. Those animals treated with 50-HB-5100 (in doses as high as 64 ml./kg.) showed no convulsions or any degree of C.N.S. stimulation. No studies with lower oral doses of the UCONS were done. Pretreatment (30 minutes) of rats with diphenylhydantoin (50 mg./kg. I.P.), atropine (20 mg./kg. I.P.),or phenobarbital (25 mg./kg. I.P.), in nonsedating doses delayed but did not prevent death caused by 1.0 ml./kg. I.P. of the 50-HB-400. Another barbiturate (pentobarbital) in nonsedative (10 mg./kg.) or hypnotic (40 mg./kg.) I.P. doses, however, does prevent the convulsions and death produced by UCON 50-HB-400. Pretreatment with meprobamate (100 mg./kg. I.P.) which inhibits convulsions produced by many spinal convulsants, did not modify the response to the UCON.

A13

Confidential

R: 5-28-62

Report 25-43

5-29-62

AFDR

tremors convulsions

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

SPECIAL REPORT

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Based on these data, (failure of diphenylhydantoin to protect presumably negates a cortical site, failure of meprobamate to protect negates a spinal site) it appears that a medullary site of action is evident. Studies into the mechanism of such stimulation were performed in anesthetized dogs with an active UCON, (UCON 50-HB-400) and an inactive one (UCON 50-HB-5100).

In one dog, deeply anesthetized with pentobarbital (40 mg./kg. I.V.), a respiratory rate of 12 per minute was recorded before injection of 0.5 ml./kg. I.P. of 50-HB-400. Within 20 minutes after injection, the respiratory rate had increased to 24 per minute. This dose would have resulted in convulsions and death had not the animal been treated with pentobarbital. In several subsequent dogs studied a characteristic pattern of effect was demonstrated:

~ 500 mg/kg the high dose

1. doses less than 50 mg./kg. exaggerated the acetylcholine depressor response (anticholinesterase action*), lowered the blood pressure, reduced the pressor response to bilateral carotid occlusion, and stimulated respiration.

2. higher doses (100-300 mg./kg.) possessed similar but more exaggerated effects, however, in addition, the pressor response to injected epinephrine was reduced; and, on occasion, reversed entirely.

* in one dog studied, a temporary inhibition of RBC cholinesterase was determined - 50 mg./kg. caused a 30% inhibition, levels were normal at 2 hours. - 100 mg./kg. caused a 45% inhibition, levels were normal at 2 hours.

low LDL - see guidance

UCON 50-HB-5100 in doses as high as 750 mg./kg. did not possess these effects.

Thus, it appears that active convulsant UCONS possess a dual mechanism of action--adrenergic blockade (direct medullary stimulation has been demonstrated for many adrenergic blocking agents) and central anticholinesterase activity. The latter effect could conceivably augment the direct stimulatory effect of the UCON, however, atropine therapy would not eliminate this direct effect which is probably the more important constituent of the convulsant action.

Morton E. Goldberg
Morton E. Goldberg, Sc.D.
Fellow

Herbert E. Johnson
Herbert E. Johnson, B.A.
Research Associate

Approved:

Charles P. Carpenter
Charles P. Carpenter, Ph.D.
Assistant Administrative Fellow

Typed: May 28, 1962 - md

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

William C. Kuryla, Ph.D.
Associate Director, Product Safety
Union Carbide Corporation
39 Old Ridgebury Road
Danbury, Connecticut 06817-0001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 18 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12122A

Triage of 8(e) Submissions

Date sent to triage: APR 20 1995

Submission number: 12122A

NON-CAP CAP

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 1 2 **pages** 1,2 **pages** 1,2,3

Notes:

Contractor reviewer : PM **Date:** 4/3/15

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0992 - 12122 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Union Carbide Corporation

SUB. DATE: 08/27/92 OTS DATE: 09/01/92 CSRAD DATE: 02/15/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0670) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:
UCON 50-HB 400
UCON 50-HB-55
UCON 50-HB-260

CAS#
9038-95-3
Unknown
" "

UCON 50-HB-5100 unknown

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
(0224)	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY
(YES)
CAS SR
NO
IN TERMINI

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT
mus
Frog
Dog

TOXICOLOGICAL CONCERN:
LOW
(MED)
HIGH

USE:

PRODUCTION:

COMMENTS: 8eha-1086-0635

No LOC assigned for i.p. route

8(E)-12122A

NO LOC WAS ASSIGNED TO THIS INTRAPERITONEAL STUDY

A LEVEL OF CONCERN WAS NOT ASSIGNED FOR ACUTE TOXICITY OF UCON 50-HB-400 BY THE INTRAPERITONEAL ROUTE IN DOGS. DOSAGES (INTRAPERITONEAL/ANETHESTIZED SUBJECT) LESS THAN 50 MG/KG EXAGGERATED THE ACETYLCHOLINE DEPRESSOR RESPONSE, LOWERED BLOOD PRESSURE, AND STIMULATED RESPIRATION. DOSES FROM 100 TO 300 MG/KG POSSESSED SIMILAR BUT MORE EXAGGERATED EFFECTS. IN ADDITION, AT THIS DOSE LEVEL THE PRESSOR RESPONSE TO INJECTED EPINEPHRINE WAS REDUCED, AND, ON OCCASION, REVERSED ENTIRELY. IN ONE DOG STUDIED, A TEMPORARY INHIBITION OF RBC CHOLINESTERASE WAS DETERMINED, 50 MG/KG CAUSED A 30% INHIBITION WITH NORMAL LEVELS AT 2 HOURS. 100 MG/KG CAUSED A 45% INHIBITION WITH NORMAL LEVELS AT 2 HOURS. IN A COMPANION STUDY WITH THE SUBJECT COMPOUND AND RELATED COMPOUNDS, POSITIVE EFFECTS WERE SEEN WITH HB-55, -260, AND -400 IN RATS AND MICE AND NEGATIVE EFFECTS SEEN WITH HB-5100 IN FEMALE MICE AND RATS. THE MINIMAL ACTIVE DOSE IN BOTH SPECIES FOR THESE COMPOUNDS WAS 0.5 ML/KG ADMINISTERED INTRAPERITONEALLY OVER A WIDE RANGE OF CONCENTRATIONS. TREMORS WERE OBSERVED AT LOWER DOSES. MORTALITY WAS NOT INDICATED. ALL FOUR COMPOUNDS WERE TESTED FOR THEIR ABILITY TO INDUCE CONVULSIVE SEIZURE AFTER ORAL ADMINISTRATION TO RATS. LETHAL DOSES WERE GIVEN TO GROUPS OF 5 ANIMALS. THOSE ANIMALS TREATED WITH HB-55, 260, AND 400 SHOWED EXCITATION OR WELL DEFINED CONVULSIONS PRECEDING DEATH. NO DOSAGES WERE INDICATED FOR THESE GROUPS. ANIMALS TREATED WITH HB-5100 IN DOSES AS HIGH AS 64 ML/KG SHOWED NO CONVULSIONS OR ANY DEGREE OF C.N.S. STIMULATION. NO STUDIES WERE DONE WITH LOWER ORAL DOSES.